12. (Amended) The method of claim 1 in which the clinical condition is selected from the group consisting of:

Parkinson's disease, Huntingdon's disease, anxiety, depression, manic depression, psychosis, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders [including anorexia and bulimia], panic attacks, withdrawal from drug abuse [including abuse of cocaine, ethanol, nicotine and benzodiazepines], schizophrenia, disorders associated with spinal trauma and/or head injury, hydrocephalus, and GI (gastrointestinal) disorders [including IBS (Irritable Bowel Syndrome)].

~~20~~ 19. (New) The method of Claim 12 in which the clinical condition is selected from anorexia, bulimia, abuse of cocaine, ethanol, nicotine, and benzodiazepines, and irritable bowel syndrome.

REMARKS

Response to Restriction Requirement. Applicants affirm the election of Group I, which now comprises Groups I – X of the original restriction requirement. The claims have been amended so that they only read on compounds of Formula I and II. Compounds of Formula I and II have not been otherwise limited, as it appears that the limitation in the earlier restriction requirement to non-cyclic amines and certain cyclic amines has been withdrawn.

Claim Rejections. The Examiner has rejected Claims 13-14 under 35 USC § 102(b) as anticipated by Fuji et al., and Claims 1, 5, and 11-12 under 35 USC § 102(b) as anticipated by Herbst '953. Various claims are rejected under 35 USC § 103(a) as obvious over Herbst, as obvious over Herbst in view of Slassi et al. (WO '516), and as over Herbst and Slassi et al. in view of Gaster et al. '122. Claim 12 is also rejected under 35 USC § 112, second paragraph, for indefinite claim language. These are all addressed below.

Rejection of Claim 12 under 35 USC § 112, second paragraph. The word "including" is objected to by the Examiner as indefinite claim language. The claim has been amended so that "including" is no longer used in the claim. New Claim 20 includes all the clinical conditions that were deleted from Claim 12. Claim 20 is therefore well supported.

Rejections under 35 USC § 102(b). The Examiner has based the rejection over Fuji et al. on an abstract, CA 118: 101,757, which shows the structural formula of 4-[2-(dipropylamino)ethyl]-1-(phenylsulfonyl)-1H-indol-6-ol, which is a compound that falls within the scope of Claims 13 and 14. The publication that is described in the abstract, Fuji, et al., Chem Pharm Bull (1992), 40(9), 2344-52, is enclosed herewith, and is also listed on enclosed Form PTO-1449. The undersigned attorney has carefully read this publication and cannot find the compound in the article. The synthesis of the indole compound without the N-arylsulfonyl group on the nitrogen of the indole (compound 34, chart 6, page 2347) is described in the paper starting in the first column of page 2347 to the first column of page 2348. Compound 34 is synthesized from Compound 40 by reduction with lithium aluminum hydride. This step is described on page 2348 in the paragraph that begins on the previous page. The step is described for reduction of the compounds 40 and 43 to compounds 34 and 44 as follows: "Treatment of these compounds with lithium aluminum hydride effected simultaneously reduction of the amide function and cleavage of the protecting group at the indole nitrogen, producing the objective compounds (34 and 44) in 77% and 75 yields." Note that if the reactions occurred in the sequence of reduction of amide to amine first, followed by removal of the arylsulfone, then the compound shown in the abstract would have been present as an unisolated intermediate. However, the author described the two reactions as occurring simultaneously in the quoted passage. This clearly indicates that Fuji et al. do not believe that the cited compound is present as even as unisolated intermediate. Furthermore, the proposed mechanism for synthesis of by-product 46, by the sequence of compound 47 yielding in first compound 48, then compound 49, and then compound 46 in the last sequence of Chart 6 described and in the first full paragraph of page 2348, is consistent with removal of the arylsulfone group before complete reduction of the amide has taken place. This suggests that the compound in the abstract is not an intermediate. The experimental description of the synthesis of compound 34 on page 2351, first column, again does not suggest intermediates.

The publication by Fuji et al, therefore, does not suggest that the arylsulfonyl compound that is shown in the abstract is present as even a transient intermediate. The publication also does not suggest a means of making and isolating the compound, if such a

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compound was desired. Finally, since the neutral compound 34 was the synthetic target, there is no reason to synthezise the arylsulfonyl indole compound, and therefore no motivation to make it.

The arylsulfonyl indole that is listed in the abstract was apparently placed in the abstract by the person who prepared the abstract for Chem Abstracts. The compound was placed in the abstract erroneously, since it is not suggested as an intermediate or product in the publication. Finally, since the compound cannot be made based on the teachings of the Fuji et al. publication, the aryl sulfonyl compound in the abstract is not enabled. It cannot be made by the teachings in the abstract or by the teachings in the abstracted publication by Fuji et al. It is respectfully submitted that this rejection should be withdrawn.

With respect to the rejection over Herbst, the Examiner has failed to appreciate the difference between the uses stated in Herbst and the uses claimed in the current application. Herbst claims that the compounds cited in the application "possess central nervous system depressant activity and anti-inflammatory activity" in the Abstract and in column 2, lines 64-65. The Examiner has incorrectly read this to be anti-depressant activity. The compounds of the instant application may be used to treat depression (Claim 12) and are therefore anti-depressants. The Herbst et al. patent and the current application teach opposite uses for the same compounds: depressant vs. anti-depressant. Therefore, the Herbst patent does not anticipate applicants' invention. It instead suggests that the compounds will not work as applicants claim. The Herbst patent, therefore, teaches away from applicants' invention.

With respect to Claims 1, 5 and 11, the utilities disclosed in Herbst et al. neither anticipate nor suggest agonism or antagonism of $5HT_6$ receptors. The receptors were not know at the time the Herbst et al. patent was written, and the utilities claimed in the Herbst et al. application (central nervous system depression and anti-inflammatory behavior) are not characteristic of a $5HT_6$ agonist or antagonist. Therefore, the disclosure of Herbst et al. would not teach one of ordinary skill in the art that compounds similar to those disclosed in Herbst et al. would have $5HT_6$ activity.

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Rejections Under 35 USC § 103(a)

Herbst '953. As explained above, one utility stated in Herbst (CNS depression) is the opposite of one of the utilities stated in the current application (anti-depressant). Since utility as an anti-depressant is characteristic of $5HT_6$ receptors, CNS depression as taught in Herbst is also contrary to applicants' claimed utility as a $5HT_6$ agonist or antagonist. Therefore, by virtue of teaching a utility opposite of the utility discovered by the applicants, Herbst teaches away from the methods of use claimed in the current application, and therefore, does not make applicants' claims obvious.

The same argument applies to compounds of formula I, which the Examiner characterizes as positional isomers of those in Herbst. The utility taught in Herbst teaches away from applicants' claimed invention for these compounds as well.

Slassi et al WO '516 in view of Herbst. As pointed out previously, Herbst teaches so strongly away from the invention that it supports arguments of non-obviousness rather than arguments of obviousness.

Slassi et al. discloses compounds in which a pyrollidine ring is attached to an indole ring by way of a methylene bridge between the 2-position of the pyrrolidine ring and the 3-position of the indole ring. These compounds are disclosed as having affinity for the $5HT_6$ receptor. This differs from the applicants' compounds in two ways; (1) The pyrollidine ring is connected at the nitrogen rather than the 2-position. This has the added effect of leaving the NH groups of the ring free, whereas the nitrogen in the applicants' compounds in which R^1 and R^2 form a pyrrolidine ring is attached to the linking group, is tertiary, and is much more sterically hindered. (2) The linking group in Slassi et al. and the linking group in applicants' compounds have different chain lengths, one carbon in Slassi, et al. and two carbons in the instant application.

This makes the compounds significantly different in terms of expected behavior. It is also well outside of the limits where homology can be us to make an argument for prima facie obviousness, since homology is only applicable for a small change in one group in a molecule. Therefore, Slassi et al. does not make applicants' claimed uses obvious.

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Herbst and Slassi et al. in view of Gaster et al '122. Herbst and Slassie et al. are discussed above. Gaster et al. is cited to support the proposition that indoline compounds are equivalent to indole compounds with respect to their binding activity with indole and indoline. In Gaster et al. a piperazine ring is bound directly to the phenyl ring of an indoline. The compounds are reported to be $5HT_{1D}$ antagonists.

This reference does not support an argument for prima facie obviousness either. First of all, the compounds in the current claims that are nearest those of Gaster et al. have a piperazine ring attached to the 4-position of an indole ring (but not an indoline ring) by a 2 or 3 carbon chain spacer. In Gaster et al., the piperazine is separated from the 6-position of the indole or indoline by a bond (i.e. they are directly attached). Thus, the spacer size is different by at least two carbons, and the benzene ring is substituted in a different position. Furthermore, the compounds of the current invention and Gaster bind to different receptors. The $5HT_{1D}$ and $5HT_6$ receptors are different with respect to the kinds of compounds that will bind to them. The Gaster et al. reference, therefore, does not add any strength to the previous arguments by the Examiner in favor of prima facie obviousness.

Summary

The three cited references are so different that they do not separately or together constitute evidence of prima facie obviousness. Herbst discloses a utility that teaches completely away from any suggestion that similar compounds may have utility as anati-depressants or $5HT_6$ agonists or antagonists. Gaster et al. and Slassi et al. both disclose compounds that differ from applicants' compounds in at least two ways structurally, so that one of skill in the art would not have a reasonable expectation that applicants' compounds would be useful as $5HT_6$ agonists or antagonists.

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It is therefore, respectfully submitted that the claims are in condition for allowance. Such action is earnestly solicited. If the Examiner wished to discuss any matter relating to this application, she is invited to telephone the undersigned at the telephone number below.

Respectfully submitted,

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Date: August 9, 2000